FIG. 1

Primary
Compound
Library

Select Route of Administration
in Mammalian System of
Interest & Barrier(s) to
Absorption

Route of Administration (Common Examples)	Mammalian System (Common Examples)	Absorption Barrier (Primary Barrier)
▫ Enteral	▫ GI Tract	▫ Lumenal Tissue-Membrane
▫ Parenteral	▫ Brain	▫ Blood Brain Barrier Tissue-Membrane
▫ Inhalation	▫ Respiratory	▫ Nasal/Lung Tissue-Membrane
▫ Transdermal	▫ Skin	▫ Epidermal/Dermal Tissue-Membrane
▫ Ocular	▫ Eye	▫ Ocular Tissue-Membrane

Select Assay/Parameters Based
on Route/Mammal/Barrier &
Generate *In vitro*
Bioavailability Data For Test
Samples From Primary Library

In vitro Bioavailability Assay/Data

Cell Culture/Tissue/Membrane
Systems/SAR/QSAR
▫ Permeability
▫ (Transport Mechanism)*

Physiological Fluid/Solvent/Buffer
Systems/SAR/QSAR
▫ Solubility
▫ (Dissolution Rate)*
*optional

FIG. 2

FIG. 3

***In vitro* Bioavailability Data**

Provide *In vitro* Bioavailability Data to PK Tool/Select PK Model For Route/Mammal/Sampling Site

PK Tool

- Input/Output System
- Simulation Engine
- Simulation Model

Generate Absorption Profile for Each Test Sample at Selected Sampling Site

Validation/ Optimization

***In vivo* Absorption Profile**

- Rate
- Extent
- Concentration

Catalogue/Rank Test Samples & Generate Secondary Library

Absorption Compound Library

FIG. 4

INPUTS	PK TOOL	OUTPUTS

INPUTS

PK Data
- *In vitro*
  - Chemical
  - Cell (sp. 1 or 2)
  - Tissue (sp. 1 or 2)
  - SAR/QSAR
- *In vivo* (sp. 1)

PK TOOL

Simulation
- Input/Output System
- Physiologic-Based Simulation Model of Selected Mammalian System & Barrier(s)
- Simulation Engine

OUTPUTS

Bioavailability/
PK Property
- *In vivo* (sp. 2)

FIG. 5

Input/Output System

Physiologic-Based Simulation Model of Selected Mammalian System Utilizing Differential Equations

Equations/Parameters
- Segment Compartments
- Segment Flow Regulators
  - Segment Converters

Underlying Equation/Parameter Values
- Segment Physiological Parameters
- Segment Correlation Parameters
- Segment Adjustment Parameters

Control Statement Rules

Simulation Engine

FIG. 6

Compartment 1   Compartment 2

Flow Regulator 1   Flow Regulator 2

Converter 2

Converter 1

FIG. 7

Symbol	Name	Time-Dependent Function
□	Compartment	Equation or value for amount of substance stored.
↦ (flow regulator symbol)	Flow Regulator	Rate equation for amount of substance transferred.
○	Converter	Equation or pre-defined value for (i) input into flow regulator; (ii) input into another converter; and/or (iii) storing value.
∿➤	Input Link	Directs input values.

FIG. 8

FIG. 9

FIG. 10

Training/Validation
Compound Set

▫ Standards
▫ Test Compounds

In vitro Data

▫ Permeability
▫ Solubility
▫ Dissolution Rate
▫ Transport Mechanism

In vivo Data

▫ IV (Intravenous) Dose
▫ Administered Route Dose

Initial Physiological
Model of Selected
Mammalian System

IV/Sample Site PK
Model

Simulated/Predicted
▫ Sample Site v. Time
▫ Plasma Level v. Time

Compare

Fitted
▫ Sample Site v. Time
▫ Plasma Level v. Time

Initial Model Building & Parameter
Development for Initial Physiological
Model of Selected Mammalian System

▫ Define Compartments & Rate Process Relations
▫ Equations
▫ Parameters/Values
▫ Rules

FIG. 11

```
┌─────────────────────────┐         ┌─────────────────────────────┐
│  Training/Validation    │         │       In vivo Data          │
│    Compound Set         │─────────▶│                             │
│                         │         │   □  IV Dose                │
│   □  Standards          │         │   □  Administered Route Dose│
│   □  Test Compounds     │         │                             │
└─────────────────────────┘         └─────────────────────────────┘
            │                                        │
            ▼                                        ▼
┌─────────────────────────┐         ┌─────────────────────────────┐
│      In vitro Data      │         │   IV/Sample Site PK Model   │
│                         │         │  ∘Analysis of in vivo data  │
│   □  Permeability       │         │  ∘Processed in vivo data    │
│   □  Solubility         │         └─────────────────────────────┘
│   □  Dissolution Rate   │                         │
│   □  Transport Mechanism│                         ▼
└─────────────────────────┘         ┌─────────────────────────────┐
            │                        │          Fitted             │
            ▼                        │  □  Sample Site v. Time     │
┌─────────────────────────┐         │  □  Plasma Level v. Time    │
│ Analysis of In vitro    │         └─────────────────────────────┘
│        Data             │                         │
└─────────────────────────┘                         ▼
            │                              ┌──────────────────┐
            ▼                              │     Compare      │
┌─────────────────────────┐               └──────────────────┘
│ Processed In vitro Data │     ┌──────────────────────┐  ┌─────────────────────────┐
└─────────────────────────┘────▶│   Optimization of    │─▶│  Simulated/Predicted    │
                                 │ Physiological Model  │  │ □  Sample Site v. Time  │
                                 └──────────────────────┘  │ □  Plasma Level v. Time │
                                           ▲               └─────────────────────────┘
                                 ┌──────────────────────┐
                                 │ Selectively Optimized│
                                 │ Adjustment Parameter │
                                 │       Values         │
                                 └──────────────────────┘
                                           ▲
                                 ┌──────────────────────┐
                                 │ Curve-Fitting Algorithm│
                                 └──────────────────────┘
                                           ▲
                                 ┌──────────────────────┐
                                 │  Physiological Model │◀─────────────────┐
                                 ├──────────────────────┤                  │
                                 │ Initial Adjustment   │◀── Empirical Values
                                 │  Parameter Values    │
                                 └──────────────────────┘
```

FIG. 12

FIG. 13

```
┌─────────────────────────────────────────────────┐
│              Mass-Volume GI Tract Model           │
│                                                   │
│  ▪ GI Segment Compartments                        │
│     ▪ Fluid Volume                                │
│     ▪ Fluid Absorption                            │
│     ▪ Insoluble Mass                              │
│     ▪ Soluble Mass Absorption                     │
│                                                   │
│  ▪ GI Segment Flow Regulators                     │
│     ▪ Fluid Volume Absorption Rate                │
│     ▪ Fluid Volume Secretion Rate                 │
│     ▪ Fluid Volume GI Transit Rate                │
│     ▪ Insoluble Mass GI Transit Rate              │
│     ▪ Soluble Mass Absorption Rate                │
│                                                   │
│  ▪ GI Segment Converters                          │
│     ▪ Rate Constant                               │
│     ▪ pH                                          │
│     ▪ Solubility                                  │
│     ▪ Surface Area                                │
│     ▪ Permeability                                │
└─────────────────────────────────────────────────┘
```

FIG. 14

```
┌─────────────────────────────────────────────────┐
│              Mass-Volume GI Tract Model           │
│                                                   │
│  ▪ GI Segment Compartments & Flow Regulators      │
│     ▪ Fluid Volume                                │
│        ▪ Fluid Volume Absorption Rate             │
│        ▪ Fluid Volume Secretion Rate             │
│        ▪ Fluid Volume GI Transit Rate            │
│     ▪ Fluid Volume Absorption                     │
│        ▪ Fluid Volume Absorption Rate             │
│        ▪ Fluid Volume Secretion Rate             │
│     ▪ Insoluble Mass                              │
│        ▪ Insoluble Mass GI Transit Rate          │
│        ▪ Soluble Mass Absorption Rate             │
│     ▪ Soluble Mass Absorption                     │
│        ▪ Soluble Mass Absorption Rate             │
└─────────────────────────────────────────────────┘
```

FIG. 15

Mass-Volume GI Tract Model

- **GI Segment Flow Regulators & *Converters***
  - **Fluid Volume Absorption Rate**
    - *Fluid Volume Absorption Rate Constant*
  - **Fluid Volume Secretion Rate**
    - *Fluid Volume Secretion Rate Constant*
  - **Fluid Volume GI Transit Rate**
    - *Fluid Volume GI Transit Rate Constant*
  - **Insoluble Mass GI Transit Rate**
    - *Insoluble Mass GI Transit Rate Constant*
  - **Soluble Mass Absorption Rate**
    - *Fluid Volume*
    - *Insoluble Mass*
    - *Mass Solubility Profile*
      - *pH*
    - *Permeability*
    - *Surface Area*

FIG. 16

Mass-Volume GI Tract Model

- **GI Segment Converters**
  - Rate Constant
  - pH
  - Solubility
  - Surface Area
  - Permeability

FIG. 17

ICM 1505 v. Mass GI Tract Model

FIG. 18

ICM 1505 v. Mass-Volume GI Tract Model

FIG. 19

FIG. 20

Training/Validation Compound Set

▫ Standards
▫ Test Compounds

In vitro Data

▫ Permeability
▫ Solubility
▫ Dissolution Rate
▫ Transport Mechanism

In vivo Data

▫ IV (Intravenous) Dose
▫ PO (Oral) Dose

Initial Physiological GI Tract Model

IV/PO PK Model

Simulated/Predicted
▫ FDp v. Time
▫ Plasma Level v. Time

Compare

Fitted
▫ FDp v. Time
▫ Plasma Level v. Time

Initial Model Building & Parameter Development for Physiological GI Tract Model

▫ Define Compartments & Rate Process Relations
▫ Equations
▫ Parameters/Values
▫ Rules

FIG. 21

Gastrointestinal Transit

FIG. 22

pH Dependent Solubility and Dissolution

FIG. 23

Absorption

FIG. 24

GI Tract –Intestinal Model

FIG. 25

GI Tract-Intestinal Model (without converters, ghosts or connectors)

FIG. 26

GI Tract-Intestinal Model

FIG. 27

FIG. 28

INPUT
Example Options For Data Input Source
▫   In vitro PK Data: Tissue; Cell; SAR/QSAR
▫   In vivo PK Data: Mammal (species 1)

Stomach	Duodenum	Jejunum	Ileum	Colon

Select Adjustment Parameters Based on Input Data Source
▫   Facilitates correlation of input variable from particular in vitro or in vivo data source to particular in vivo output variable

FIG. 29

INPUT
▫   Minimum of one Regional Permeability (Pe) Value

Stomach	Duodenum	Jejunum	Ileum	Colon

Regional Permeability (Pe) Correlation
(Rulebase Logic Function)
▫   Polynomial equation/calculation
▫   Estimate other regional Pe's from input of one or more other regional Pe values

FIG. 30

Parameters

VOL PARM   SURFACE AREA   DOSE   INIT VOLUM

VOL ADJ   SA ADJ   TIME IN HOURS   pH

PARACELLULAR

FIG. 31

Transit Time

TRANSFERS   CUMU TT

TRANSIT ADJ   ADJ TRANSIT TIME

USER TT INPUT

FIG. 32

Permeability Calculation

ACT PE

FLUX ADJ   ADJ PERM

Km

EFFLUX ADJ

PASS PE   REGIONAL

CARRIER ADJ

CONCENTRATIONS

RC   RCSUM

FIG. 33

Solubility Calculation

USER pH

ADJ SOLUB

USER SOLUB

pH

FIG. 34

Control Release Calculation

CR RATE

CR DOSE

CR AT TIME   CR AT LAST

FIG. 35

Concentration Calculation

VOL 1   VOL 2   VOL 3   VOL 4   VOL 5

CONCENTRATIONS   ADJ SOLUB

SOL 1   SOL 2   SOL 3   SOL 4   SOL 5

FIG. 36

Dissolution Calculation

FIG. 37

ABSORPTION 2   ABSORPTION 3

ABSORBED TOTAL   FDp%   DOSE

ABSORPTION 4   ABSORPTION 5

FIG. 38

FLUX TOTAL

FLUX 2   FLUX 3   FLUX 4   FLUX 5

FIG. 39

CUM DISS

DISS PRECIP 1

CUMM DISS RATE

DISS PRECIP 2

DISS PRECIP 3   DISS PRECIP 4   DISS PRECIP

FIG. 40

CR INPUT 3   CR INPUT 2   CR INPUT 1   CR INPUT 5

CR Release

CR INPUT 4

CR cumrate

FIG. 41

Physiological GI Tract Model

Database
- **GI Segment Compartments**
  - Fluid Absorption
  - Fluid Volume
  - Insoluble Mass
  - Soluble Mass
  - Soluble Mass Absorption
  - Dosage Form Mass

- **GI Segment Flow Regulators**
  - Fluid Absorption Rate
  - Fluid Volume Transit Rate
  - Insoluble Mass Transit Rate
  - Insoluble Mass Dissolution Rate
  - Soluble Mass Transit Rate
  - Soluble Mass Absorption Rate
  - Dosage Form Disintegration/Release Rate

- **GI Segment Converters**
  - Fluid Volume Absorption Rate Constant
  - GI Transit Rate Constant
  - Adjusted Dissolution Rate Constant
  - Dissolved Drug Concentration
  - Adjusted Surface Area
  - Adjusted Permeability

Rulebase
- GI Transit
- Dissolution
- Absorption
- Permeability Calculations
- Concentration Calculations
- Computational Error Corrections

FIG. 42

Physiological GI Tract Model

- GI Segment Compartments & *Flow Regulators*
  - Fluid Absorption
    - *Fluid Absorption Rate*
  - Fluid Volume
    - *Fluid Volume Absorption Rate*
    - *Fluid Volume Transit Rate*
  - Insoluble Mass
    - *Insoluble Mass Transit Rate*
    - *Insoluble Mass Dissolution Rate*
  - Soluble Mass
    - *Insoluble Mass Dissolution Rate*
    - *Soluble Mass Transit Rate*
    - *Soluble Mass Absorption Rate*
  - Soluble Mass Absorption
    - *Soluble Mass Absorption Rate*

FIG. 43

Physiological GI Tract Model

- GI Segments Flow Regulators & *Converters*
  - Fluid Absorption Rate
    - *Fluid Volume*
    - *Fluid Volume Absorption Rate Constant*
  - Fluid Volume Transit Rate
    - *Fluid Volume*
    - *Fluid Volume Transit Rate Constant*
  - Insoluble Mass Transit Rate
    - *Insoluble Mass*
    - *Insoluble Mass Transit Rate Constant*
  - Insoluble Mass Dissolution Rate
    - *Insoluble Mass*
    - *Dissolution Rate Constant*
  - Soluble Mass Transit Rate
    - *Soluble Mass*
    - *Soluble Mass Transit Rate Constant*
  - Soluble Mass Absorption Rate (Flux)
    - *Surface Area*
    - *Dissolved Mass Concentration*
    - *Permeability*

FIG. 44

Physiological GI Tract Model

- **Converters**
  - Permeability
    - Passive Absorption Adjustment Parameter
      - Efflux/Secretion Adjustment Parameter
      - Active Absorption Adjustment Parameter
      - Active or Carrier Mediated Absorptive Permeability
      - Km
      - Passive Permeability/Regional Correlation
        - Passive Permeability
        - Logic Function For Regional Correlation
          - Passive Permeability
          - Logic Function For Regional Correlation
      - Dissolved Mass Concentrations
  - Dissolved Mass Concentration
    - Fluid Volume
    - Solubility
      - pH
      - Solubility
  - Dissolution Rate Constant
    - Fluid Volume
    - Precipitation Rate Constant
    - Dissolution Rate Adjustment Parameter
    - Solubility
    - Insoluble Mass
    - Soluble Mass
  - Surface Area
    - Surface Area Adjustment Parameter
    - Transport Mechanism
  - Transit Rate
    - Transit Time Adjustment Parameter
    - User Adjusted Transit Time
  - Fluid Volume Absorption Rate Constant
   - Fluid Volume Adjustment Parameter

FIG. 45

INPUTS		OUTPUTS

INPUTS

- Dose
- Permeability
- Solubility
- Dissolution Rate
- Transport Mechanism
- Transit Rate
- pH
- Controlled Release Rate
- Other

PK TOOL

OUTPUTS

- Rate of Absorption
- Extent of Absorption
- Regional Concentration
- Other

FIG. 46

Select Model

Model Database

Physiological
GI Tract Model

Parameter Database

In vitro

In vivo

Select Tissue   Select SAR/QSAR   Select Cell   Select Mammal

FIG. 47

Simulation Engine

Physiological
GI Tract Model

Start

I/O

Dose

Permeability

Solubility

Dissolution Rate

Transport Mechanism

Transit Time

pH

Formulation Release
Rate

Menu

Start Simulation

Stop Simulation

Rate of Absorption

Extent of Absorption

Concentration

Print Graph

Print Table

Quit

FIG. 48

FIG. 49

Correlation of FDp Extent - GI Model andPharmacokinetic data

FIG. 50

Correlation of FDp rate of absorption – GI Model and
Pharmacokinetic Data
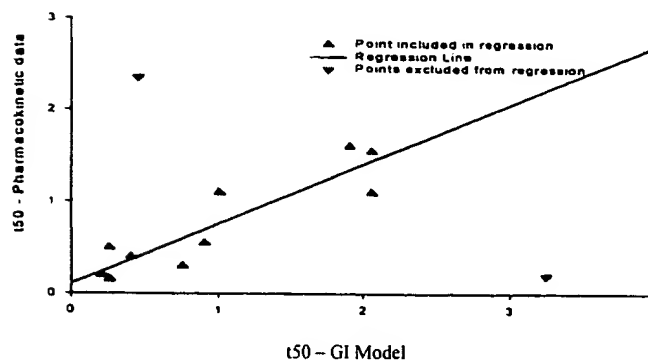
FIG. 51

PO Pharmacokinetic Data
Compound α 1

---- Input From PK Fitting
—— Input From GI- Model
● Oral Data

FIG. 52

PO Pharmacokinetic Data
Compound α 4

---- Input From PK Fitting
—— Input From GI- Model
● Oral Data

FIG. 53

PO Pharmacokinetic Data
Compound β 6

- - - - Input From PK Fitting
——— Input From GI- Model
● Oral Data

FIG. 54

INPUT		PK TOOL	OUTPUT	
COMPOUND •SAR •QSAR	PK DATA •Permeability •Dissolution •Solubility •Other		ABSORPTION •Rate •Extent •Concentration •Other	COMPOUND •CAD •CAE

FIG. 55

COMPOUND •Synthesis	IN VITRO SCREENING •Absorption •Activity •Metabolism •Toxicity	PK TOOL

DATABASE
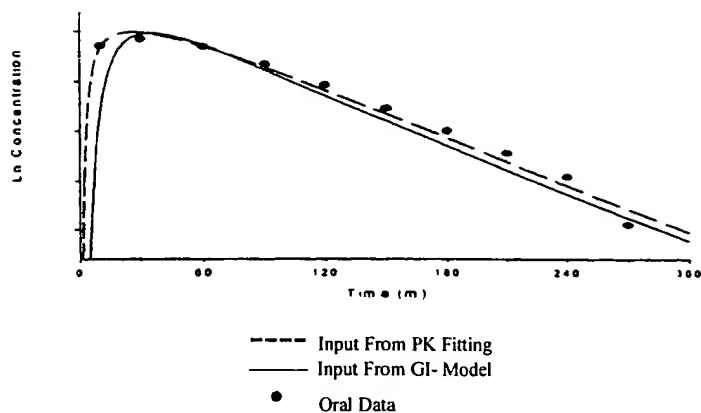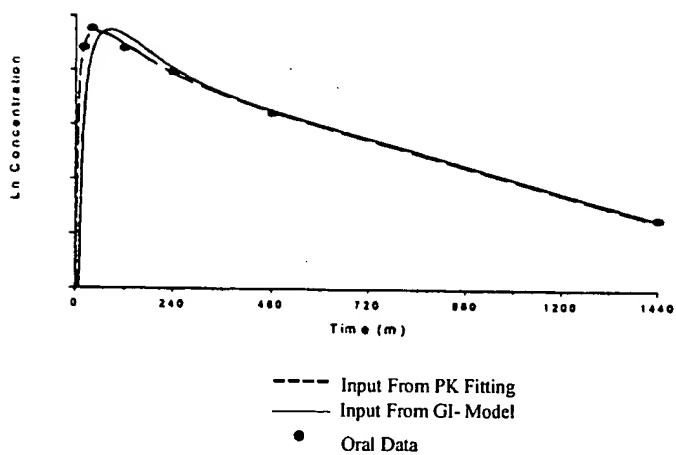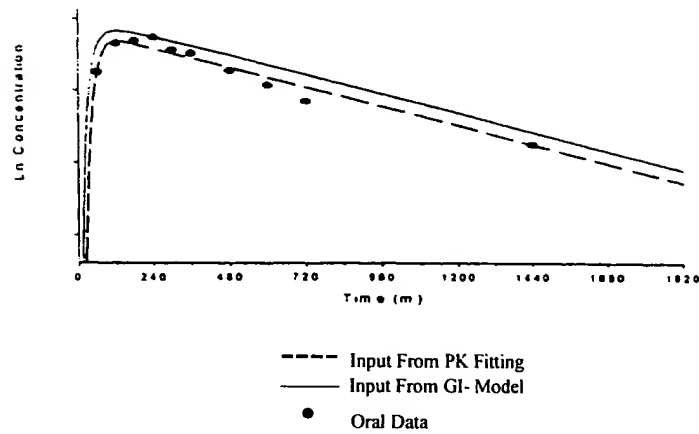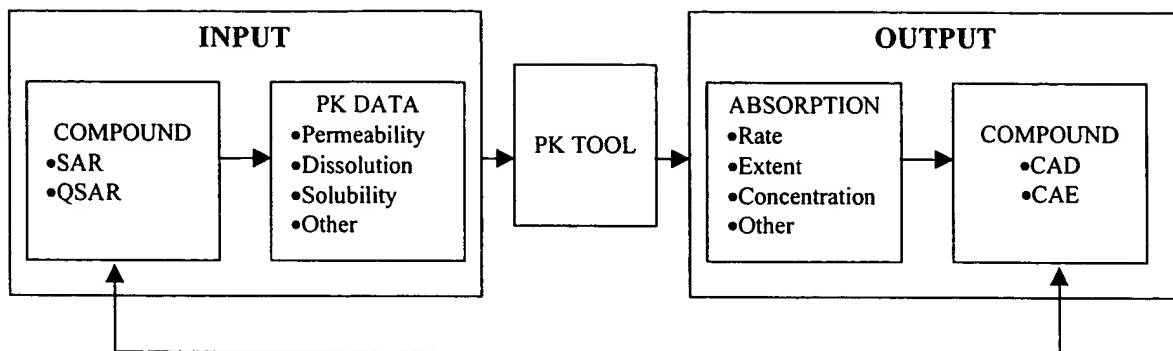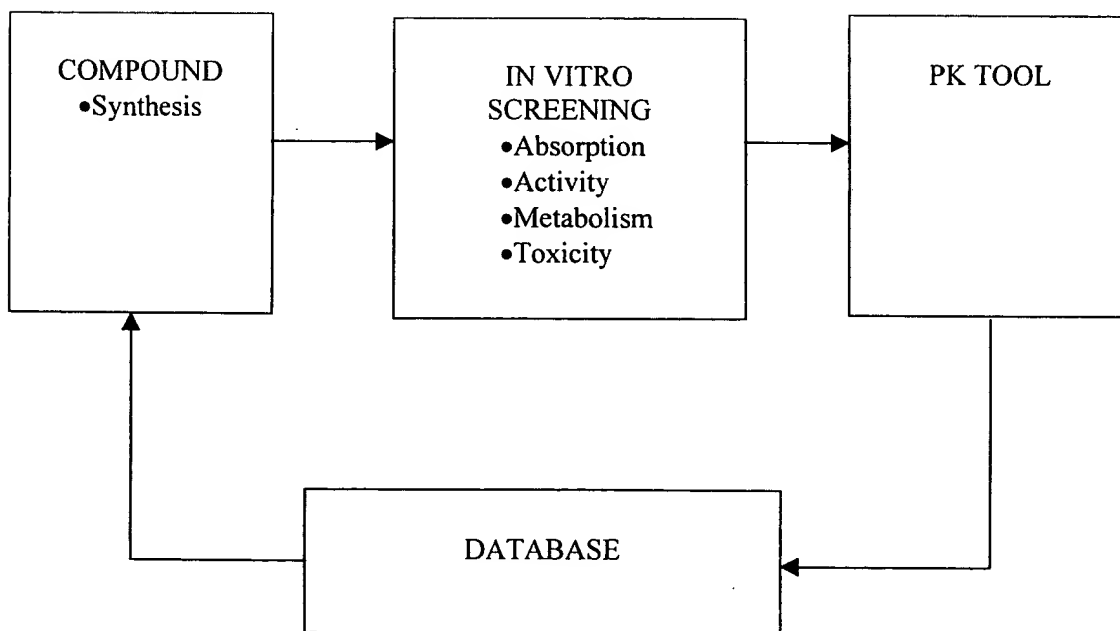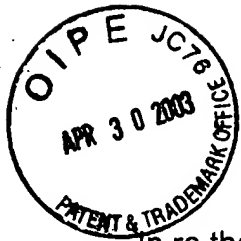
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

GRASS et al.

Application No.: 09/786,362

Filed: June 25, 2001

Confirmation No.: 6261

Art Unit: 1631

Examiner: Ly, Cheyne D.

Attorney Dkt. No.: 109904-00028

For: METHOD FOR SCREENING AND PRODUCING COMPOUND LIBRARIES

SUBMISSION OF FORMAL DRAWINGS

Commissioner for Patents
Washington, DC 20231

April 30, 2003

Sir:

In response to the Notice of Reply Not Fully Responsive to Prior Office Action dated April 1, 2003 and the Office Action (Restriction Requirement) dated January 31, 2003 attached hereto new formal drawings to replace corresponding sheets containing the informal drawings objected to. It is respectfully submitted that Figs. 1-55 overcome the objections to the originally filed drawings.

If any fees are required with respect to this paper, please charge our Deposit Account No. 01-2300 referring to client-matter number 109904-00028.

Respectfully submitted,

Rustan J. Hill
Registration No. 37,351

1050 Connecticut Avenue, N.W., Suite 400
Washington, D.C. 20036-5339
Tel (202) 857-6000
Fax (202) 638-4810
RJH/sh

Enclosures: Formal Drawings (Figs. 1-55, 36 Sheets)

FIG. 1

Primary Compound Library

Select Route of Administration in Mammalian System of Interest & Barrier(s) to Absorption

---

Route of Administration (Common Examples)	Mammalian System (Common Examples)	Absorption Barrier (Primary Barrier)
▪ Enteral	▪ GI Tract	▪ Lumenal Tissue-Membrane
▪ Parenteral	▪ Brain	▪ Blood Brain Barrier Tissue-Membrane
▪ Inhalation	▪ Respiratory	▪ Nasal/Lung Tissue-Membrane
▪ Transdermal	▪ Skin	▪ Epidermal/Dermal Tissue-Membrane
▪ Ocular	▪ Eye	▪ Ocular Tissue-Membrane

Select Assay/Parameters Based on Route/Mammal/Barrier & Generate *In vitro* Bioavailability Data For Test Samples From Primary Library

---

***In vitro* Bioavailability Assay/Data**

Cell Culture/Tissue/Membrane Systems/SAR/QSAR
▪ Permeability
▪ (Transport Mechanism)*

Physiological Fluid/Solvent/Buffer Systems/SAR/QSAR
▪ Solubility
▪ (Dissolution Rate)*
*optional

FIG. 2

```
                    ┌─────────────────────┐
                    │ Administration Site │
                    └─────────────────────┘
                              │
                              ▼
                    ┌─────────────────────┐
                    │   Primary Barrier   │
                    │    to Absorption    │
                    └─────────────────────┘
                              │
                              ▼
                    ┌─────────────────────┐
                    │   Sampling Site     │
                    └─────────────────────┘
                              │
                              ▼
                    ┌─────────────────────┐
                    │  Secondary Barrier  │
                    │    to Absorption    │
                    └─────────────────────┘
                              │
                              ▼
                    ┌─────────────────────┐
                    │   Sampling Site     │
                    └─────────────────────┘
```

FIG. 3

In vitro Bioavailability Data

Provide *In vitro*
Bioavailability Data to PK
Tool/Select PK Model For
Route/Mammal/Sampling
Site

PK Tool

- Input/Output System
- Simulation Engine
- Simulation Model

Generate Absorption
Profile for Each Test
Sample at Selected
Sampling Site

**Validation/
Optimization**

In vivo Absorption Profile

- Rate
- Extent
- Concentration

Catalogue/Rank Test
Samples & Generate
Secondary Library

**Absorption
Compound
Library**

FIG. 4

INPUTS	PK TOOL	OUTPUTS
PK Data	**Simulation**	**Bioavailability/ PK Property**
□ *In vitro*	□ Input/Output System	□ *In vivo* (sp. 2)
□ Chemical	□ Physiologic-Based Simulation Model of Selected Mammalian System & Barrier(s)	
□ Cell (sp. 1 or 2)		
□ Tissue (sp. 1 or 2)		
□ SAR/QSAR	□ Simulation Engine	
□ *In vivo* (sp. 1)		

FIG. 5

Input/Output System

Physiologic-Based Simulation Model of Selected Mammalian System Utilizing Differential Equations

Equations/Parameters
    □   **Segment Compartments**
□ **Segment Flow Regulators**
    □   **Segment Converters**

Underlying Equation/Parameter Values
    □ **Segment Physiological Parameters**
    □ **Segment Correlation Parameters**
    □ **Segment Adjustment Parameters**

Control Statement Rules

Simulation Engine

FIG. 6

Compartment 1   Compartment 2

Flow Regulator 1   Flow Regulator 2

Converter 2

Converter 1

FIG. 7

Symbol	Name	Time-Dependent Function
▢	Compartment	Equation or value for amount of substance stored.
⟶ (flow regulator symbol)	Flow Regulator	Rate equation for amount of substance transferred.
○	Converter	Equation or pre-defined value for (i) input into flow regulator; (ii) input into another converter; and/or (iii) storing value.
∿➤	Input Link	Directs input values.

FIG. 8


```
┌─────────────────────┐   k10    ┌─────────────────────┐
│  Central/Plasma     │ ───────► │  Elimination/Waste  │
│  Compartment 1      │          │  Compartment 0      │
│  Dp, Vp, Cp         │          │                     │
└─────────────────────┘          └─────────────────────┘
    │        ▲
  k12       k21
    ▼        │
┌─────────────────────┐
│  Peripheral/Tissue  │
│  Compartment 2      │
│  Dt, Vt, Ct         │
└─────────────────────┘
```

FIG. 9

FIG. 10

Training/Validation Compound Set

- Standards
- Test Compounds

***In vitro* Data**

- Permeability
- Solubility
- Dissolution Rate
- Transport Mechanism

***In vivo* Data**

- IV (Intravenous) Dose
- Administered Route Dose

Initial Physiological Model of Selected Mammalian System

IV/Sample Site PK Model

Simulated/Predicted
- Sample Site v. Time
- Plasma Level v. Time

Compare

Fitted
- Sample Site v. Time
- Plasma Level v. Time

Initial Model Building & Parameter Development for Initial Physiological Model of Selected Mammalian System

- Define Compartments & Rate Process Relations
- Equations
- Parameters/Values
- Rules

FIG. 11

```
┌─────────────────────────┐          ┌──────────────────────────┐
│   Training/Validation    │          │       In vivo Data       │
│     Compound Set         │─────────▶│                          │
│                          │          │  ▫  IV Dose              │
│  ▫  Standards            │          │  ▫  Administered Route   │
│  ▫  Test Compounds       │          │       Dose               │
└─────────────────────────┘          └──────────────────────────┘
             │                                    │
             ▼                                    ▼
┌─────────────────────────┐          ┌──────────────────────────┐
│     In vitro Data        │          │  IV/Sample Site PK Model │
│                          │          │  ○Analysis of in vivo    │
│  ▫  Permeability         │          │     data                 │
│  ▫  Solubility           │          │  ○Processed in vivo data │
│  ▫  Dissolution Rate     │          └──────────────────────────┘
│  ▫  Transport Mechanism  │                     │
└─────────────────────────┘                     ▼
             │                         ┌──────────────────────────┐
             ▼                         │         Fitted           │
┌─────────────────────────┐           │  ▫  Sample Site v. Time  │
│  Analysis of In vitro    │           │  ▫  Plasma Level v. Time │
│         Data             │           └──────────────────────────┘
└─────────────────────────┘                     │
             │                                   ▼
             ▼                         ┌──────────────────────┐
┌─────────────────────────┐           │      Compare         │
│ Processed In vitro Data  │           └──────────────────────┘
└─────────────────────────┘                     │
       │                                         ▼
       │   ┌──────────────────────┐    ┌──────────────────────────┐
       └──▶│   Optimization of    │───▶│   Simulated/Predicted    │
           │ Physiological Model  │    │  ▫  Sample Site v. Time  │
           └──────────────────────┘    │  ▫  Plasma Level v. Time │
                      ▲                 └──────────────────────────┘
           ┌──────────────────────┐
           │ Selectively Optimized│
           │ Adjustment Parameter │
           │       Values         │
           └──────────────────────┘
                      ▲
           ┌──────────────────────┐
           │ Curve-Fitting        │
           │    Algorithm         │
           └──────────────────────┘
                      ▲
           ┌──────────────────────┐
           │  Physiological Model │◀─────┐
           ├──────────────────────┤      │
           │ Initial Adjustment   │◀──┐  │
           │  Parameter Values    │   │  │
           └──────────────────────┘   │  │
                              ┌────────────────────┐
                              │  Empirical Values  │
                              └────────────────────┘
```

FIG. 12

FIG. 13

Mass-Volume GI Tract Model

- **GI Segment Compartments**
  - Fluid Volume
  - Fluid Absorption
  - Insoluble Mass
  - Soluble Mass Absorption

- **GI Segment Flow Regulators**
  - Fluid Volume Absorption Rate
  - Fluid Volume Secretion Rate
  - Fluid Volume GI Transit Rate
  - Insoluble Mass GI Transit Rate
  - Soluble Mass Absorption Rate

- **GI Segment Converters**
  - Rate Constant
  - pH
  - Solubility
  - Surface Area
  - Permeability

FIG. 14

Mass-Volume GI Tract Model

- **GI Segment Compartments & *Flow Regulators***
  - **Fluid Volume**
    - *Fluid Volume Absorption Rate*
    - *Fluid Volume Secretion Rate*
    - *Fluid Volume GI Transit Rate*
  - **Fluid Volume Absorption**
    - *Fluid Volume Absorption Rate*
    - *Fluid Volume Secretion Rate*
  - **Insoluble Mass**
    - *Insoluble Mass GI Transit Rate*
    - *Soluble Mass Absorption Rate*
  - **Soluble Mass Absorption**
    - *Soluble Mass Absorption Rate*

FIG. 15

```
Mass-Volume GI Tract Model

▪ GI Segment Flow Regulators & Converters
    ▪ Fluid Volume Absorption Rate
        ▪ Fluid Volume Absorption Rate Constant
    ▪ Fluid Volume Secretion Rate
        ▪ Fluid Volume Secretion Rate Constant
    ▪ Fluid Volume GI Transit Rate
        ▪ Fluid Volume GI Transit Rate Constant
    ▪ Insoluble Mass GI Transit Rate
        ▪ Insoluble Mass GI Transit Rate Constant
    ▪ Soluble Mass Absorption Rate
        ▪ Fluid Volume
        ▪ Insoluble Mass
        ▪ Mass Solubility Profile
            ▪ pH
        ▪ Permeability
        ▪ Surface Area
```

FIG. 16

```
Mass-Volume GI Tract Model

▪ GI Segment Converters
    ▪ Rate Constant
    ▪ pH
    ▪ Solubility
    ▪ Surface Area
    ▪ Permeability
```

FIG. 17

ICM 1505 v. Mass GI Tract Model

FIG. 18

ICM 1505 v. Mass-Volume GI Tract Model

FIG. 19

FIG. 20

```
                    ┌─────────────────────────┐
                    │  Training/Validation     │
                    │  Compound Set            │
                    │                          │
                    │  ▪ Standards             │
                    │  ▪ Test Compounds        │
                    └─────────────────────────┘
```

┌─────────────────────────┐   ┌─────────────────────────┐
│ *In vitro* **Data**   │   │ *In vivo* **Data**   │
│   │   │   │
│ ▪ Permeability   │   │ ▪ IV (Intravenous) Dose │
│ ▪ Solubility   │   │ ▪ PO (Oral) Dose   │
│ ▪ Dissolution Rate   │   │   │
│ ▪ Transport Mechanism   │   │   │
└─────────────────────────┘   └─────────────────────────┘

┌─────────────────────────┐   ┌─────────────────────────┐
│ **Initial Physiological**│   │ **IV/PO PK Model**   │
│ **GI Tract Model**   │   │   │
└─────────────────────────┘   └─────────────────────────┘

┌─────────────────────────┐ ┌──────────┐ ┌─────────────────────────┐
│ **Simulated/Predicted**│ │ Compare │ │   **Fitted**   │
│ ▪ FDp v. Time   │ └──────────┘ │ ▪ FDp v. Time   │
│ ▪ Plasma Level v. Time │   │ ▪ Plasma Level v. Time │
└─────────────────────────┘   └─────────────────────────┘

┌──────────────────────────────────┐
│ **Initial Model Building & Parameter** │
│ **Development for**   │
│ **Physiological GI Tract Model** │
│   │
│ ▪ Define Compartments & Rate   │
│   Process Relations   │
│ ▪ Equations   │
│ ▪ Parameters/Values   │
│ ▪ Rules   │
└──────────────────────────────────┘

FIG. 21

Gastrointestinal Transit

FIG. 22

pH Dependent Solubility and Dissolution

FIG. 23

Absorption

FIG. 24

GI Tract –Intestinal Model

FIG. 25

GI Tract-Intestinal Model (without converters, ghosts or connectors)

FIG. 26

GI Tract-Intestinal Model

FIG. 27

in-vitro Data

Permeability - Dissolution
Solubility – Transport Mechanism

Human in-vivo
PK Data
(IV & PO)

IV/PO
PK Model

Dissolution
Analysis

Permeability
Analysis

Physiological
Intestinal Model

Intestinal pH
Intestinal Surface Area
Water Flux

Analysis of PK Data
(Fitting)

Analysis of
in-vitro Data

Processed
in-vitro Data

Physio-Chemical
Equations

Dissolution etc.

Fitted
FDp v. Time
Plasma Level v. time

Compare

Initial
Adjustment
Parameters

Predicted
FDp v. Time
Plasma Level v. time

Initial GI
Model

Optimization
of
GI Model
(Simultaneous Fitting)

Optimized
Adjustment
Parameters

Input

Processed
in-vitro Data

**Optimized
GI Model**

Output

Predicted
FDp v. Time
Plasma Level v. time

FIG. 28

INPUT
Example Options For Data Input Source
▫ In vitro PK Data: Tissue; Cell; SAR/QSAR
▫ In vivo PK Data: Mammal (species 1)

Stomach	Duodenum	Jejunum	Ileum	Colon

Select Adjustment Parameters Based on Input Data Source
▫ Facilitates correlation of input variable from particular in vitro or in vivo data source to particular in vivo output variable

FIG. 29

INPUT
▫ Minimum of one Regional Permeability (Pe) Value

Stomach	Duodenum	Jejunum	Ileum	Colon

Regional Permeability (Pe) Correlation
(Rulebase Logic Function)
▫ Polynomial equation/calculation
▫ Estimate other regional Pe's from input of one or more other regional Pe values

FIG. 30

Parameters

VOL PARM   SURFACE AREA   DOSE   INIT VOLUM

VOL ADJ   SA ADJ   TIME IN HOURS   pH

PARACELLULAR

FIG. 31

Transit Time

TRANSFERS   CUMU TT

TRANSIT ADJ   ADJ TRANSIT TIME

USER TT INPUT

FIG. 32

Permeability Calculation

FIG. 33

Solubility Calculation

FIG. 34

Control Release Calculation

CR RATE

CR DOSE

CR AT TIME   CR AT LAST

FIG. 35

Concentration Calculation

VOL 1   VOL 2   VOL 3   VOL 4   VOL 5

CONCENTRATIONS   ADJ SOLUB

SOL 1   SOL 2   SOL 3   SOL 4   SOL 5

FIG. 36

Dissolution Calculation

VOL 1   VOL 2   VOL 3   VOL 4   VOL 5

PRECIP   DISSOL

DISS ADJ

ADJ DISS PRECIP

ADJ SOLUB

SOL 1   SOL 2   SOL 3   SOL 4   SOL 5   MASS 1   MASS 2   MASS 3   MASS 4   MASS 5

FIG. 37

ABSORPTION 2 ABSORPTION 3

ABSORBED TOTAL FDp% DOSE

ABSORPTION 4 ABSORPTION 5

FIG. 38

FLUX TOTAL

FLUX 2 FLUX 3 FLUX 4 FLUX 5

FIG. 39

CUM DISS

DISS PRECIP 1

CUMM DISS RATE

DISS PRECIP 2

DISS PRECIP 3 DISS PRECIP 4 DISS PRECIP

FIG. 40

CR INPUT 3   CR INPUT 2   CR INPUT 1   CR INPUT 5

CR Release

CR INPUT 4

CR cumrate

FIG. 41

Physiological GI Tract Model

Database
- **GI Segment Compartments**
  - Fluid Absorption
  - Fluid Volume
  - Insoluble Mass
  - Soluble Mass
  - Soluble Mass Absorption
  - Dosage Form Mass

- **GI Segment Flow Regulators**
  - Fluid Absorption Rate
  - Fluid Volume Transit Rate
  - Insoluble Mass Transit Rate
  - Insoluble Mass Dissolution Rate
  - Soluble Mass Transit Rate
  - Soluble Mass Absorption Rate
  - Dosage Form Disintegration/Release Rate

- **GI Segment Converters**
  - Fluid Volume Absorption Rate Constant
  - GI Transit Rate Constant
  - Adjusted Dissolution Rate Constant
  - Dissolved Drug Concentration
  - Adjusted Surface Area
  - Adjusted Permeability

Rulebase
- GI Transit
- Dissolution
- Absorption
- Permeability Calculations
- Concentration Calculations
- Computational Error Corrections

FIG. 42

Physiological GI Tract Model

- **GI Segment Compartments & *Flow Regulators***
  - **Fluid Absorption**
    - *Fluid Absorption Rate*
  - **Fluid Volume**
    - *Fluid Volume Absorption Rate*
    - *Fluid Volume Transit Rate*
  - **Insoluble Mass**
    - *Insoluble Mass Transit Rate*
    - *Insoluble Mass Dissolution Rate*
  - **Soluble Mass**
    - *Insoluble Mass Dissolution Rate*
    - *Soluble Mass Transit Rate*
    - *Soluble Mass Absorption Rate*
  - **Soluble Mass Absorption**
    - *Soluble Mass Absorption Rate*

FIG. 43

Physiological GI Tract Model

- **GI Segments Flow Regulators & *Converters***
  - **Fluid Absorption Rate**
    - *Fluid Volume*
    - *Fluid Volume Absorption Rate Constant*
  - **Fluid Volume Transit Rate**
    - *Fluid Volume*
    - *Fluid Volume Transit Rate Constant*
  - **Insoluble Mass Transit Rate**
    - *Insoluble Mass*
    - *Insoluble Mass Transit Rate Constant*
  - **Insoluble Mass Dissolution Rate**
    - *Insoluble Mass*
    - *Dissolution Rate Constant*
  - **Soluble Mass Transit Rate**
    - *Soluble Mass*
    - *Soluble Mass Transit Rate Constant*
  - **Soluble Mass Absorption Rate (Flux)**
    - *Surface Area*
    - *Dissolved Mass Concentration*
    - *Permeability*

FIG. 44

Physiological GI Tract Model

- **Converters**
  - Permeability
    - Passive Absorption Adjustment Parameter
      - Efflux/Secretion Adjustment Parameter
      - Active Absorption Adjustment Parameter
      - Active or Carrier Mediated Absorptive Permeability
      - Km
      - Passive Permeability/Regional Correlation
        - Passive Permeability
        - Logic Function For Regional Correlation
          - Passive Permeability
          - Logic Function For Regional Correlation
      - Dissolved Mass Concentrations
  - Dissolved Mass Concentration
    - Fluid Volume
    - Solubility
      - pH
      - Solubility
  - Dissolution Rate Constant
    - Fluid Volume
    - Precipitation Rate Constant
    - Dissolution Rate Adjustment Parameter
    - Solubility
    - Insoluble Mass
    - Soluble Mass
  - Surface Area
    - Surface Area Adjustment Parameter
    - Transport Mechanism
  - Transit Rate
    - Transit Time Adjustment Parameter
    - User Adjusted Transit Time
  - Fluid Volume Absorption Rate Constant
   - Fluid Volume Adjustment Parameter

FIG. 45

INPUTS	PK TOOL	OUTPUTS

INPUTS

- Dose
- Permeability
- Solubility
- Dissolution Rate
- Transport Mechanism
- Transit Rate
- pH
- Controlled Release Rate
- Other

PK TOOL

OUTPUTS

- Rate of Absorption
- Extent of Absorption
- Regional Concentration
- Other

FIG. 46

Select Model

Model Database

Physiological
GI Tract Model

Parameter Database

In vitro   *In vivo*

Select Tissue   Select SAR/QSAR   Select Cell   Select Mammal

FIG. 47

FIG. 48

Colon	Colon	Colon	Colon
Jejunum	Jejunum	Jejunum	Jejunum
Ileum	Ileum	Ileum	Ileum
Duodenum	Duodenum	Duodenum	Duodenum
Stomach	Stomach	Stomach	Stomach
Solubility	Permeability	Dissolution Rate	Transit Time

Menu

Transport Mechanism	Dose	Formulation Release Rate	pH
Passive Paracellular	Multiple Dosing	Stomach	Stomach
Passive Transcellular		Duodenum	Duodenum
Carrier-Mediated Influx		Ileum	Ileum
Carrier-Mediated Efflux		Jejunum	Jejunum
		Colon	Colon

FIG. 49

Correlation of FDp Extent - GI Model andPharmacokinetic data

FDp predicted – GI Model

FIG. 50

Correlation of FDp rate of absorption – GI Model and
Pharmacokinetic Data

t50 – GI Model

FIG. 51

PO Pharmacokinetic Data
Compound α 1

---- Input From PK Fitting
——— Input From GI- Model
● Oral Data

FIG. 52

PO Pharmacokinetic Data
Compound α 4

---- Input From PK Fitting
——— Input From GI- Model
● Oral Data

FIG. 53

PO Pharmacokinetic Data
Compound β 6

- - - - Input From PK Fitting
——— Input From GI- Model
● Oral Data

FIG. 54

INPUT		PK TOOL	OUTPUT	
COMPOUND •SAR •QSAR	PK DATA •Permeability •Dissolution •Solubility •Other		ABSORPTION •Rate •Extent •Concentration •Other	COMPOUND •CAD •CAE

FIG. 55

COMPOUND
•Synthesis

IN VITRO SCREENING
•Absorption
•Activity
•Metabolism
•Toxicity

PK TOOL

DATABASE